Perinatal asphyxia

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ABSTRACT

INTRODUCTION: In resource-rich countries, the incidence of severe perinatal asphyxia (causing death or severe neurological impairment) is about 1/1000 live births. In resource-poor countries, perinatal asphyxia is probably much more common. Data from hospital-based studies in such settings suggest an incidence of 5–10/1000 live births. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions in term or near-term newborns with perinatal asphyxia? We searched: Medline, Embase, The Cochrane Library and other important databases up to June 2006 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 25 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: anticonvulsants (prophylactic), antioxidants, calcium channel blockers, corticosteroids, fluid restriction, head and/or whole body hypothermia, hyperbaric oxygen treatment, hyperventilation, inotrope support, magnesium sulphate, mannitol, opiate antagonists, and resuscitation (in air versus higher concentrations of oxygen).

QUESTIONS

INTERVENTIONS

Key points

- Estimates of the incidence of perinatal asphyxia vary. In resource-rich countries, severe perinatal asphyxia (causing death or severe neurological impairment) is 1/1000 live births; in resource-poor countries, studies suggest an incidence of 5–10/1000 live births.
- Limited evidence from three small, weak RCTs suggests that mortality may be lower in infants treated with antioxidants compared with placebo.
- There is limited evidence that hypothermia reduces mortality and neurodevelopmental disability in infants with perinatal asphyxia.
- Limited evidence from one small RCT suggests that a magnesium sulphate/dopamine combination may be more effective than no treatment in reducing a combined outcome of mortality, abnormal scans, and failure to feed.
- Small RCTs with flawed methods suggest that anticonvulsants are of no benefit in reducing mortality or improving neurodevelopmental outcomes in term infants with perinatal asphyxia.
- Resuscitation in air lowered mortality in infants with perinatal asphyxia compared with resuscitation in 100% oxygen. However, current clinical practice is to use 100% oxygen.
- Limited evidence from a systematic review that reported problems with publication bias in the RCTs it identified suggests that hyperbaric oxygen treatment lowers rates of mortality and adverse neurological outcomes in infants with perinatal asphyxia and hypoxic–ischaemic encephalopathy. This treatment, although widely used in China, is not standard practice in other countries.
- We don't know whether calcium channel blockers, corticosteroids, fluid restriction, hyperventilation, inotrope support, mannitol, or opiate antagonists are helpful in infants with perinatal asphyxia.

DEFINITION

The clinical diagnosis of perinatal asphyxia is based on several criteria, the two main ones being evidence of cardiorespiratory and neurological depression (defined as an Apgar score remaining less than 7 at 5 minutes after birth) and evidence of acute hypoxic compromise with acidaemia (defined as an arterial blood pH of less than 7 or base excess greater than 12 mmol/L). [1] In many

settings, especially resource-poor countries, it may be impossible to assess fetal or neonatal acidaemia. In the immediate postpartum period when resuscitation is being undertaken, it may not be possible to determine whether the neurological and cardiorespiratory depression is secondary to hypoxia–ischaemia, or to another condition such as feto-maternal infection, or metabolic disease. Consequently, resuscitation and early management will often be of suspected rather than confirmed perinatal asphyxia. [2] [3] [4] This review deals with perinatal asphyxia in term and near-term newborns.

INCIDENCE/ PREVALENCE

Estimates of the incidence of perinatal asphyxia vary depending on the definitions used. In resource-rich countries, the incidence of severe perinatal asphyxia (causing death or severe neurological impairment) is about 1/1000 live births. [5] [6] In resource-poor countries, perinatal asphyxia is probably much more common. Data from hospital-based studies in such settings suggest an incidence of 5–10/1000 live births. [7] [8] [9] However, this probably represents an underestimate of the true community incidence of perinatal asphyxia in resource-poor countries.

AETIOLOGY/ RISK FACTORS

Perinatal asphyxia may occur *in utero*, during labour and delivery, or in the immediate postnatal period. There are numerous causes, including placental abruption, cord compression, transplacental anaesthetic or narcotic administration, intrauterine pneumonia, severe meconium aspiration, congenital cardiac or pulmonary anomalies, and birth trauma. Postnatal asphyxia can be caused by an obstructed airway, maternal opiates — which can cause respiratory depression — or congenital sepsis.

PROGNOSIS

Worldwide, perinatal asphyxia is a major cause of death and of acquired brain damage in newborn infants. [9] The prognosis depends on the severity of the asphyxia. Only a minority of infants with severe encephalopathy after perinatal asphyxia survive without handicap. [5] However, there are limited population-based data on long-term outcomes after perinatal asphyxia, such as cerebral palsy, developmental delay, visual and hearing impairment, and learning and behavioural problems. After an asphyxial event, there may be an opportunity to intervene to minimise brain damage. The first phase of brain damage — early cell death — results from primary exhaustion of the cellular energy stores. Early cell death can occur within minutes. Immediate resuscitation to restore oxygen supply and blood circulation aims to limit the extent of this damage. A secondary phase of neuronal injury may occur several hours after the initial insult. The mechanisms believed to be important in this process include oxygen free radical production, intracellular calcium entry, and apoptosis. Treatments during the postresuscitation phase aim to block these processes, thereby limiting secondary cell damage and minimising the extent of any brain damage.

AIMS OF INTERVENTION

To minimise mortality, and brain and other organ damage, with minimal adverse effects.

OUTCOMES

Mortality: treatment failure measured by rates of death before hospital discharge. **Neurological impairment**: includes incidence of neurodevelopmental disability assessed at greater than 12 months of age using a validated tool, and severity of hypoxic–ischaemic encephalopathy assessed using a validated tool.

METHODS

Clinical Evidence search and appraisal March 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2007, Embase 1980 to March 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and the National Institute of Health and Clinical Excellence (NICE). Abstracts of studies retrieved from the initial search were assessed independently by two information specialists. Predetermined criteria were used to identify relevant studies. Study design criteria for inclusion in this review were: systematic reviews, RCTs, and quasi-randomised studies. Open trials were included because blinding was not possible for all interventions; however, those assessing neurological deficit were blind to treatment group. Small trials (fewer than 20 people) and trials with less than 80% follow-up were included. There was no minimum length of follow-up. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 21). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice

may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions in term or near-term newborns with perinatal asphyxia?**

OPTION **ANTIOXIDANTS**

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- Limited evidence from three small, weak RCTs suggests that mortality may be lower in infants treated with antioxidants compared with placebo.

Benefits and harms

Allopurinol versus placebo or no drug treatment:

We found one systematic review (search date not reported) [10] that identified one small RCT, [11] and we found two subsequent RCTs. [12] [13]

Mortality

Allopurinol compared with placebo Allopurinol seems more effective than placebo at reducing mortality in infants with perinatal asphyxia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[11] RCT	22 term neonates with asphyxia In review [10]	**Death** 2/11 (18%) with allopurinol (40 mg/kg) 6/11 (55%) with no drug treatment	RR 0.73 95% CI 0.26 to 2.09	⟷	Not significant
[11] RCT	22 term neonates with asphyxia In review [10]	**Rates of death or developmental delay (method of assessment not reported)** 4/11 (36%) with allopurinol (40 mg/kg) 7/11 (64%) with no drug treatment	RR 0.57 95% CI 0.23 to 1.41	⟷	Not significant
[12] RCT	32 term neonates with severe asphyxia	**Death** 13/17 (77%) with allopurinol (iv 40 mg/kg; 2 doses) 10/15 (67%) with placebo Allopurinol iv 40 mg/kg: 2 doses, first dose as soon as possible after birth, the second dose 12 hours later The trialists have not yet reported long-term outcomes	RR 1.15 95% CI 0.74 to 1.79	⟷	Not significant
[13] RCT	60 term neonates with mild, moderate, or severe asphyxia	**Death** 3/30 (10%) with allopurinol (40 mg/kg/day for 3 days) 3/30 (10%) with placebo	RR 1.00 95% CI 0.22 to 4.56	⟷	Not significant

Neurological impairment

Allopurinol compared with placebo Allopurinol may be no more effective than placebo at reducing the risk of neurological impairment in infants with perinatal asphyxia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological impairment					
[13] RCT	60 term neonates with mild, moderate, or severe asphyxia	**Incidence of severe neurological impairment , >12 months after birth** 38/27 (30%) with allopurinol (40 mg/kg/day for 3 days) 12/27 (44%) with placebo Cerebral palsy, cortical blindness, deafness, or severe developmental delay	RR 0.67 95% CI 0.33 to 1.37	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [11] [12] [13]

Miltiorrhizae versus citicoline (cytidine diphosphate choline):

We found one systematic review (search date not reported), which identified one small RCT comparing two antioxidants versus each other. [10] The RCT compared miltiorrhizae (a Chinese herb with antioxidant properties) versus citicoline (also an antioxidant). [14]

Mortality

Miltiorrhizae compared with citicoline (*cytidine diphosphate choline*) Miltiorrhizae (a Chinese herb with antioxidant properties) may be more effective than citicoline at reducing the rate of a composite outcome of death and neurological development in infants with perinatal asphyxia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[14] RCT	63 neonates with perinatal asphyxia, unclear if near term or term In review [10]	**Mortality or neurological abnormality** 6/35 (17%) with miltiorrhizae 13/28 (46%) with citicoline Mortality or neurological abnormality assessed using the Chinese neonatal behavioural neurological assessment scores; no further details reported	R 0.37 95% CI 0.16 to 0.81	●●○	miltiorrhizae

Neurological impairment

No data from the following reference on this outcome. [14]

Adverse effects

No data from the following reference on this outcome. [14]

Further information on studies

[10] The systematic review cautioned that both of the RCTs it identified gave insufficient information on allocation concealment, method of randomisation, and blinding of assessors to determine trial quality and validity of the findings.

Comment: **Clinical guide:**
Free radicals are recognised as an important cause of brain damage in infants who have suffered an asphyxial injury. [15] In theory, antioxidants might therefore prevent free radical neuronal damage after perinatal asphyxia.

OPTION CALCIUM CHANNEL BLOCKERS

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- We don't know whether calcium channel blockers are helpful in infants with perinatal asphyxia.
- The use of calcium channel blockers has been associated with clinically important hypotension in severely asphyxiated newborn infants.

Benefits and harms

Calcium channel blockers:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
The use of calcium channel blockers has been associated with clinically important hypotension in severely asphyxiated newborn infants. [16] In one small case series, four term infants with asphyxia received a continuous infusion of nicardipine. The heart rate increased in all four infants, and mean arterial blood pressure fell in three. Two infants had a sudden and marked fall in blood pressure, together with severe impairment of skin blood flow and a concurrent fall in cerebral blood flow. [16]

OPTION CORTICOSTEROIDS

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- We found no direct information about the effects of corticosteroids in the treatment of infants with perinatal asphyxia.
- We don't know whether corticosteroids are helpful in infants with perinatal asphyxia.

Benefits and harms

Corticosteroids:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although corticosteroids may reduce cerebral oedema, data from studies in older children or adults with cerebral hypoxia, and from animal studies, suggest that corticosteroids do not improve neurological outcomes. [17] [18] In a small case series of newborn infants with birth asphyxia treated with dexamethasone, there was no evidence of an effect on cerebral perfusion pressure. [19]

OPTION FLUID RESTRICTION

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- We found no direct information about the effects of fluid restriction in the treatment of infants with perinatal asphyxia.
- We don't know whether fluid restriction is helpful in infants with perinatal asphyxia.

Benefits and harms

Fluid restriction:

We found one systematic review (search date 2004), which identified no RCTs assessing the effects of fluid restriction in term newborns with perinatal asphyxia. [20]

Further information on studies

Comment: **Clinical guide:**
Current recommendations to restrict fluid input are based mainly on data from the treatment of adults and older children, or from animal models of cerebral hypoxia. [21] The rationale is that fluid restriction may limit cerebral oedema, which may be important in the pathogenesis of brain damage after perinatal asphyxia. However, there is concern that excessive fluid restriction may cause dehydration and hypotension, resulting in decreased cerebral perfusion and further brain damage.

OPTION HEAD AND/OR WHOLE-BODY HYPOTHERMIA

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- There is limited evidence that hypothermia reduces mortality and neurodevelopmental disability in infants with perinatal asphyxia.

Benefits and harms

Head, and whole-body, hypothermia versus normothermia:

We found one systematic review (search date 2003, 2 RCTs) [22] and three subsequent RCTs. [23] [24] [25]

Mortality

Head, and whole-body, hypothermia compared with normothermia Head, and whole-body, hypothermia seems more effective than normothermia at reducing mortality or composite outcomes of death and severe disability in infants with perinatal asphyxia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[22] Systematic review	50 term infants with moderate/severe neonatal encephalopathy and	**Mortality** 5/27 (19%) with hypothermia 6/23 (26%) with normothermia	RR 0.73 95% CI 0.26 to 2.09	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	evidence of intrapartum asphyxia 2 RCTs in this analysis				
[23] RCT	67 term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Mortality** 10/32 (31%) with systemic hypothermia 14/33 (42%) with normothermia Systemic hypothermia: 33°C for 48 hours within 6 hours after birth	RR 0.74 95% CI 0.38 to 1.41	⟷	Not significant
[24] RCT	234 newborn infants with clinical and electroencephalographic evidence of moderate or severe neonatal (hypoxic–ischaemic) encephalopathy	**Death , at 18 months** 36/108 (33%) with therapeutic cooling of the infant's head and mild systemic hypothermia 42/110 (38%) with normothermia	RR 0.87 95% CI 0.61 to 1.25	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Mortality** 24/102 (24%) with whole-body cooling 37/106 (35%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 0.68 95% CI 0.44 to 1.05	⟷	Not significant
[22] Systematic review	23 term infants with moderate/severe neonatal encephalopathy and evidence of intrapartum asphyxia Data from 1 RCT	**Combined outcome of death or major neurodevelopmental disability** 7/18 (39%) with hypothermia 4/13 (31%) with normothermia	RR 1.26 95% CI 0.46 to 3.44	⟷	Not significant
[24] RCT	234 newborn infants with clinical and electroencephalographic evidence of moderate or severe neonatal (hypoxic–ischaemic) encephalopathy	**Combined outcome of death or severe disability , at 18 months** 59/108 (55%) with therapeutic cooling of the infant's head and mild systemic hypothermia 73/110 (66%) with normothermia	RR 0.82 95% CI 0.66 to 1.02	⟷	Not significant
[24] RCT	Subgroup analysis of 46 infants with severe amplitude-integrated electroencephalographic findings at enrollment Subgroup analysis	**Combined outcome of death or severe disability , at 18 months** 19/24 (79%) with therapeutic cooling of the infant's head and mild systemic hypothermia 15/22 (68%) with normothermia	RR 1.16 95% CI 0.82 to 1.65	⟷	Not significant
[24] RCT	Subgroup analysis of 172 infants with intermediate amplitude integrated electroencephalographic changes Subgroup analysis	**Combined outcome of death or severe disability , at 18 months** 40/84 (48%) with therapeutic cooling of the infant's head and mild systemic hypothermia 58/88 (66%) with normothermia	RR 0.72 95% CI 0.55 to 0.95 NNT 6 95% CI 3 to 25	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Death or moderate/severe disability , at 18–24 months** 45/102 (44%) with whole-body cooling 64/106 (60%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 0.73 95% CI 0.56 to 0.95 NNT 6 95% CI 3 to 33	●○○	hypothermia

Neurological impairment

Head, and whole-body, hypothermia compared with normothermia Head, and whole-body, hypothermia is no more effective than normothermia at reducing in neurological impairment in infants with perinatal asphyxia (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological impairment					
[22] Systematic review	23 term infants with moderate/severe neonatal encephalopathy and evidence of intrapartum asphyxia Data from 1 RCT	**Major neurodevelopmental disability** 4/13 (31%) with hypothermia 1/10 (10%) with normothermia	RR 3.08 95% CI 0.40 to 23.44	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Rate of moderate or severe disability in survivors** 21/78 (27%) with whole-body cooling 26/68 (38%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 0.70 95% CI 0.44 to 1.13	⟷	Not significant

No data from the following reference on this outcome. [23] [24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] Systematic review	31 infants Data from 1 RCT	**Sinus bradycardia** with hypothermia with normothermia Absolute results not reported	RR 2.21 95% CI 0.1 to 50.3	⟷	Not significant
[22] Systematic review	31 infants 2 RCTs in this analysis	**Need for inotrope support** with hypothermia with normothermia Absolute results not reported	RR 2.41 95% CI 0.82 to 7.08	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] Systematic review	31 infants Data from 1 RCT	**Anaemia requiring blood transfusion** with hypothermia with normothermia Absolute results not reported	RR 3.68 95% CI 0.19 to 70.9	⟷	Not significant
[22] Systematic review	31 infants Data from 1 RCT	**Hypokalaemia** with hypothermia with normothermia Absolute results not reported	RR 1.16 95% CI 0.49 to 2.73	⟷	Not significant
[22] Systematic review	31 infants Data from 1 RCT	**Oliguria** with hypothermia with normothermia Absolute results not reported	RR 0.67 95% CI 0.22 to 2.03	⟷	Not significant
[22] Systematic review	31 infants Data from 1 RCT	**Coagulopathy resulting in major thrombosis or haemorrhage** with hypothermia with normothermia Absolute results not reported	RR 3.68 95% CI 0.19 to 70.9	⟷	Not significant
[22] Systematic review	31 infants Data from 1 RCT	**Culture-proven sepsis** with hypothermia with normothermia Absolute results not reported	RR 0.72 95% CI 0.05 to 10.52	⟷	Not significant
[23] RCT	67 term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Bradycardia** 11/31 (35%) with systemic hypothermia 2/31 (6%) with normothermia Systemic hypothermia 33°C for 48 hours within 6 hours after birth	RR 5.5 95% CI 1.33 to 22.8	●●●	normothermia
[23] RCT	67 term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Plasma transfusions for coagulopathy** 23/31 (74%) with systemic hypothermia 11/31 (35%) with normothermia Systemic hypothermia 33°C for 48 hours within 6 hours after birth	RR 2.09 95% CI 1.25 to 3.51	●●○	normothermia
[23] RCT	67 term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Mean duration of inotrope support** 5 days with systemic hypothermia 2 days with normothermia Systemic hypothermia 33°C for 48 hours within 6 hours after birth	P = 0.02	○○○	normothermia
[24] RCT	234 newborn infants with clinical and electroencephalographic evidence of moderate or severe neonatal (hypoxic–ischaemic) encephalopathy	**Sinus bradycardia** 10/112 (9%) with therapeutic cooling of the infant's head and mild systemic hypothermia 1/118 (1%) with normothermia	RR 10.5 95% CI 1.37 to 80.97	●●●	normothermia

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[24] RCT	234 newborn infants with clinical and electroencephalographic evidence of moderate or severe hypoxic–ischaemic encephalopathy	**Hypotension** 62/112 (55%) with therapeutic cooling of the infant's head and mild systemic hypothermia 61/118 (52%) with normothermia	RR 1.07 95% CI 0.84 to 1.36	⟷	Not significant
[24] RCT	234 newborn infants with clinical and electroencephalographic evidence of moderate or severe hypoxic–ischaemic encephalopathy	**Coagulopathy** 21/112 (19%) with therapeutic cooling of the infant's head and mild systemic hypothermia 17/118 (14%) with normothermia	RR 1.30 95% CI 0.73 to 2.34	⟷	Not significant
[24] RCT	234 newborn infants with clinical and electroencephalographic evidence of moderate or severe hypoxic–ischaemic encephalopathy	**Renal impairment** 73/112 (65%) with therapeutic cooling of the infant's head and mild systemic hypothermia 83/118 (70%) with normothermia	RR 0.93 95% CI 0.77 to 1.11	⟷	Not significant
[24] RCT	234 newborn infants with clinical and electroencephalographic evidence of moderate or severe hypoxic–ischaemic encephalopathy	**Hypoglycaemia** 14/112 (13%) with therapeutic cooling of the infant's head and mild systemic hypothermia 20/118 (17%) with normothermia	RR 0.74 95% CI 0.39 to 1.39	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Hypotension treated with vasopressors** 42/112 (38%) with whole-body cooling 35/118 (30%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 1.26 95% CI 0.88 to 1.82	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Cardiac arrhythmia** 2/112 (2%) with whole-body cooling 1/118 (1%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 2.11 95% CI 0.19 to 22.9	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Persistent pulmonary hypertension** 25/112 (22%) with whole-body cooling 23/118 (19%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 1.15 95% CI 0.69 to 1.90	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Renal impairment** 22/112 (20%) with whole-body cooling 27/118 (23%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 0.86 95% CI 0.52 to 1.42	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Hypoglycaemia** 12/112 (11%) with whole-body cooling 16/118 (14%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 0.79 95% CI 0.39 to 1.60	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Hypocalcaemia** 28/112 (25%) with whole-body cooling 20/118 (17%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 1.47 95% CI 0.88 to 2.46	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Hepatic dysfunction** 20/112 (18%) with whole-body cooling 16/118 (14%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 1.32 95% CI 0.72 to 2.41	⟷	Not significant
[25] RCT	208 term or near-term infants with moderate/severe neonatal encephalopathy after perinatal asphyxia	**Disseminated intravascular coagulopathy** 18/112 (16%) with whole-body cooling 12/118 (10%) with normothermia Whole-body cooling (oesophageal temperature 33.5°C for 72 hours) administered within 6 hours after birth and continued for 72 hours with usual care	RR 1.58 95% CI 0.80 to 3.13	⟷	Not significant

Further information on studies

[23] Although the RCT evaluated neurodevelopmental disability as an outcome, we have not included these data, because 23% of surviving infants did not have neurodevelopmental assessment owing to loss to follow-up.

Comment:

Clinical guide:
The possibility that therapeutic cooling of the encephalopathic newborn infant's brain may limit delayed neuronal death has been considered for more than 40 years. [26] Experimental studies using animal models have shown that lowering the core temperature by about 3°C after a hypoxic–ischaemic insult reduces the neuronal metabolic rate and the level of secondary cellular energy failure. [27] [28] In addition to the recently completed trials mentioned above, several large RCTs of therapeutic hypothermia for newborn infants with hypoxic–ischaemic encephalopathy are currently in progress. [22] They investigate the effect of direct head cooling (plus moderate systemic hypothermia), or whole-body cooling sufficient to lower brain core temperature by about 3°C. Once these data are available, a systematic review and meta-analysis (if appropriate) may provide a more precise estimate of treatment effect. [23] Currently, head and/or whole-body hypothermia is not recommended outside the context of controlled clinical trials. [29]

OPTION HYPERBARIC OXYGEN TREATMENT

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- Limited evidence, from a systematic review that reported problems with publication bias in the RCTs it identified, suggests that hyperbaric oxygen treatment lowers rates of mortality and adverse neurological outcomes in infants with perinatal asphyxia and hypoxic–ischaemic encephalopathy. This treatment, although widely used in China, is not standard practice in other countries.

Benefits and harms

Hyperbaric oxygen treatment:

We found one systematic review (search date 2004, 20 RCTs and quasi-RCTs, all undertaken in China and reported in the Chinese medical literature). [30]

Mortality

Hyperbaric oxygen treatment compared with control Hyberbaric oxygen treatment may be more effective than control at reducing mortality in infants with perinatal asphyxia and hypoxic–ischaemic encephalopathy (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[30] Systematic review	675 infants with evidence of perinatal asphyxia and hypoxic–ischaemic encephalopathy 7 RCTs in this analysis	**Mortality** 15/348 (4%) with hyperbaric oxygen 51/327 (16%) with control	OR 0.26 95% CI 0.14 to 0.46	●●○	hyperbaric oxygen

Neurological impairment

Hyperbaric oxygen treatment compared with control Hyberbaric oxygen treatment may be more effective than control at reducing neurological impairment (developmental delay, epilepsy, mental retardation, cerebral palsy, or a combination) in infants with perinatal asphyxia and hypoxic–ischaemic encephalopathy (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological impairment					
[30] Systematic review	675 infants with evidence of perinatal asphyxia and hypoxic–ischaemic encephalopathy 7 RCTs in this analysis	**Rate of adverse neurological sequelae** 43/332 (13%) with hyperbaric oxygen 84/317 (26%) with control Rate of adverse neurological sequelae — developmental delay, epilepsy, mental retardation, cerebral palsy, or a combination	OR 0.41 95% CI 0.27 to 0.61	●●○	hyperbaric oxygen

Adverse effects

No data from the following reference on this outcome. [30]

Further information on studies

[30] The findings should be interpreted with caution. The weaknesses in the trial methods included quasi-randomisation, lack of allocation concealment or blinding of outcome measurement, incompleteness, and short length of follow-up. It is also possible that publication bias resulted from selective publication of trials indicating that hyperbaric oxygen therapy improves outcomes.

Comment: **Clinical guide:**
Hyperbaric oxygen is widely used for treating infants with hypoxic–ischaemic encephalopathy in China, but is not a standard practice in other countries.

OPTION HYPERVENTILATION

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- We found no direct information from RCTs about the effects of hyperventilation in the treatment of infants with perinatal asphyxia.
- We don't know whether hyperventilation is helpful in infants with perinatal asphyxia.

Benefits and harms

Hyperventilation:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Hyperventilation-induced hypocapnia causes cerebral vasoconstriction. [31] Although this might be associated with a compensatory increase in oxygen extraction in the brain, vasoconstriction may potentially worsen regional cerebral ischaemia.

OPTION INOTROPE SUPPORT

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- We don't know whether inotrope support is helpful in infants with perinatal asphyxia.

Benefits and harms

Inotrope support versus placebo:

We found one systematic review (search date 2002), which found no RCTs of sufficient size to assess the effects of dopamine or other inotropic agents in infants with perinatal asphyxia. [32]

Inotrope support plus magnesium sulphate:
See option on magnesium sulphate, p 14

Further information on studies

Comment: **Clinical guide:**
More research is needed on the effect of inotrope support for infants who are hypotensive after perinatal asphyxia.

OPTION MAGNESIUM SULPHATE

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- Limited evidence from one small RCT suggests that a magnesium sulphate/dopamine combination may be more effective than no treatment in reducing a combined outcome of mortality, abnormal scans, and failure to feed.

Benefits and harms

Magnesium sulphate :

We found one systematic review (search date not reported), which identified no RCTs. [10]

Magnesium sulphate plus inotrope support versus no drug treatment:

We found one small RCT which compared magnesium sulphate infusion 250 mg/kg daily plus dopamine 5 micrograms/kg/minute infusion versus no drug treatment for 3 days. [33]

Mortality

Magnesium sulphate plus inotrope support compared with no drug treatment Magnesium sulphate plus dopamine is no more effective at reducing mortality at three days, but may be more effective at reducing a composite adverse outcome of death, abnormal cranial computerised tomography and electroencephalography results, and the failure to establish oral feeding at three days in infants with severe birth asphyxia, compared with no drug treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[33] RCT	33 near-term or term infants with severe birth asphyxia	**Mortality** 2/17 (12%) with magnesium sulphate (250 mg/kg daily) plus dopamine (5 micrograms/kg/minute) 1/16 (6%) with no drug treatment	RR 1.88 95% CI 0.19 to 18.8	⟷	Not significant
[33] RCT	33 near-term or term infants with severe birth asphyxia	**Incidence of a composite adverse outcome** 5/17 (29%) with magnesium sulphate (250 mg/kg daily) plus dopamine (5 micrograms/kg/minute) 11/16 (69%) with no drug treatment	RR 0.43 95% CI 0.19 to 0.96 NNT 2.6 95% CI 1.4 to 12.5	●●○	magnesium sulphate plus dopamine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Composite outcome included — death, or abnormal cranial computerised tomography and electroencephalography results, or failure to establish oral feeding by 14 days of age			

Neurological impairment

No data from the following reference on this outcome. [33]

Adverse effects

No data from the following reference on this outcome. [33]

Further information on studies

Comment: None.

OPTION MANNITOL

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- We don't know whether mannitol is helpful in infants with perinatal asphyxia.

Benefits and harms

Mannitol versus no drug treatment:

We found one small RCT, which compared mannitol (a single dose of 1 g/kg) versus no drug treatment. [34]

Mortality

Mannitol compared with no drug treatment A single dose of mannitol seems no more effective than no treatment at reducing mortality rates in neonates with asphyxia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[34] RCT	25 term neonates with asphyxia	**Mortality** 4/12 (33%) with mannitol (single dose 1 g/kg) 4/13 (31%) with no drug treatment	RR 1.08 95% CI 0.35 to 3.40	⟷	Not significant

Neurological impairment

No data from the following reference on this outcome. [34]

Adverse effects

No data from the following reference on this outcome. [34]

Further information on studies

Comment: None.

OPTION OPIATE ANTAGONISTS

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- We don't know whether opiate antagonists are helpful in infants with perinatal asphyxia.

Benefits and harms

Opiate antagonists:

We found one systematic review (search date 2003), which identified no RCTs assessing the outcomes of interest. [35]

Further information on studies

Comment: The systematic review [35] identified one RCT (193 term infants with 1-minute Apgar scores 6 or lower), which compared intramuscular naloxone (about 0.4 mg/kg) versus placebo (saline solution injection) but did not assess mortality or neurodevelopmental outcomes. [36] It found no significant difference between treatments in respiratory rate and heart rate at 24 hours after birth (significance assessment not reported). However, it found that naloxone improved active muscle tone of upper and lower limbs compared with placebo (data reported graphically, at 5 minutes: P <0.05). The RCT gave no information on adverse effects.

OPTION RESUSCITATION IN AIR VERSUS PURE OXYGEN

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .
- Resuscitation in air lowered mortality in infants with perinatal asphyxia compared with resuscitation in 100% oxygen. However, current clinical practice is to use 100% oxygen.

Benefits and harms

Resuscitation in air versus pure oxygen:

We found one systematic review (5 RCTs) comparing resuscitation in air versus resuscitation using 100% oxygen.

Mortality

Resuscitation in air compared with 100% oxygen Resuscitation in air may be more effective than 100% oxygen at reducing mortality in infants (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[37] Systematic review	1737 term and preterm infants with low Apgar scores at birth 5 RCTs in this analysis	**Mortality** 69/881 (8%) with air 111/856 (13%) with 100% oxygen	OR 0.59 95% CI 0.48 to 0.74 See further information on studies regarding interpretation of this result	●○○	air
[37] Systematic review	1502 term infants with low Apgar scores at birth 5 RCTs in this analysis Subgroup analysis	**Mortality** 44/762 (6%) with air 70/740 (9%) with 100% oxygen	OR 0.59 95% CI 0.40 to 0.87 P = 0.008 See further information on studies regarding interpretation of this result	●○○	air

Neurological impairment

No data from the following reference on this outcome. [37]

Adverse effects

No data from the following reference on this outcome. [37]

Further information on studies

[37] These findings should be interpreted with caution because of weaknesses in the methods used in some of the original trials — such as quasi-randomisation, lack of allocation concealment or blinding of outcome measurement, incompleteness, and short length of follow-up.

Comment:

Clinical guide:
Current standard practice is to resuscitate infants with neurological and cardiorespiratory depression using 100% oxygen, with the aim of reversing hypoxia rapidly. However, there is some evidence from preclinical and animal studies to suggest that resuscitating infants using lower inspired oxygen concentrations (including air) may be as effective as 100% oxygen. [38] There is also some evidence that using lower concentrations of oxygen limits oxidative stress and secondary neuronal death. [15] Although the above systematic reviews indicate that mortality is lower if air rather than 100% oxygen is used, these findings should be interpreted with caution because of weaknesses in the methods used in some of the original trials — such as quasi-randomisation, lack of allocation concealment or blinding of outcome measurement, incompleteness, and short length of follow-up.

OPTION ANTICONVULSANTS (PROPHYLACTIC)

- For GRADE evaluation of interventions for Perinatal asphyxia, see table, p 21 .

- Small RCTs with flawed methods suggest that anticonvulsants are of no benefit in reducing mortality or improving neurodevelopmental outcomes in term infants with perinatal asphyxia.

Benefits and harms

Prophylactic anticonvulsants versus no drug treatment:

We found one systematic review (search date 2001, 3 RCTs) and one subsequent RCT. [39] [40]

Mortality

Prophylactic anticonvulsants compared with no drug treatment Thiopental or phenobarbital may be no more effective than no drug treatment at reducing mortality in term infants with perinatal asphyxia, and in near-term infants with hypoxic–ischaemic encephalopathy (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[39] Systematic review	110 term infants 3 RCTs in this analysis	**Mortality** 12/58 (21%) with barbiturate (thiopental or phenobarbital) 10/52 (19%) with no drug treatment	RR 1.06 95% CI 0.50 to 2.27	⟷	Not significant
[40] RCT	45 asphyxiated neonates (gestational age 34 weeks and over) manifesting hypoxic–ischaemic encephalopathy in the first 6 hours of life	**Mortality** 5/25 (20%) with prophylactic phenobarbital (20 mg/kg given within 6 hours after birth 3/20 (15%) with standard treatment	RR 1.33 95% CI 0.36 to 4.92	⟷	Not significant

Neurological impairment

Prophylactic anticonvulsants compared with no drug treatment We don't know whether thiopental or phenobarbital are more effective than no treatment at reducing neurological disabilities in term infants with perinatal asphyxia. Phenobarbital may be more effective at reducing the risk of seizures in near-term infants with hypoxic–ischaemic encephalopathy (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological impairment					
[39] Systematic review	77 surviving term infants 3 RCTs in this analysis	**Rates of severe neurodevelopmental disability** 9/40 (23%) with barbiturate (thiopental or phenobarbital) 14/37 (38%) with no drug treatment	RR 0.61 95% CI 0.30 to 1.22	⟷	Not significant
[40] RCT	45 asphyxiated neonates (gestational age 34 weeks and over) manifesting hypoxic–ischaemic encephalopathy in the first 6 hours of life	**Proportion of infants who developed seizures** 2/25 (8%) with prophylactic phenobarbital (20 mg/kg given within 6 hours after birth) 8/20 (40%) with standard treatment	RR 0.20 95% CI 0.05 to 0.84 NNT 3.1 95% CI 1.8 to 12.5	●●○	phenobarbital

Adverse effects

No data from the following reference on this outcome. [39] [40]

Further information on studies

[39] The RCTs identified in the systematic review were small and used weak methods, including lack of allocation concealment, lack of blinding, and lack of placebo control.

Comment: **Clinical guide:**
Although prophylactic anticonvulsant therapy may reduce the frequency of seizures in infants following perinatal asphyxia, there is no evidence that mortality or longer-term neurodevelopmental outcomes are affected.

GLOSSARY

Apgar score Quantitative score, usually measured at 1, 5, and 10 minutes after birth. The infant's heart rate, respiratory effort, muscle tone, response to stimulation (usually pharyngeal suctioning), and colour are assessed. For each of these five components, assessors award a maximum of 2 points for normal, 1 point for poor, and 0 points for bad. An Apgar score of less than 7 indicates moderate neuro/cardiorespiratory depression, and a score of less than 3 indicates severe depression. The Apgar score is less reliable in premature infants, in whom it directly correlates with gestation.

Moderate vision loss Loss of three or more lines of distance vision measured on a special eye chart, corresponding to a doubling of the visual angle.

Near term Greater than 34 completed weeks' gestation and less than 37 weeks' gestation. (i.e. 35 and 36 weeks' gestation)

Term Greater than 36 completed weeks' gestation.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Hypoxic–ischaemic encephalopathy (neonatal encephalopathy) An abnormal neurobehavioural state in newborn infants, which is described clinically by stages. Stage 1 (mild): hyperalertness, hyper-reflexia, dilated pupils, tachycardia, and absence of seizures. Stage 2 (moderate): lethargy, hyper-reflexia, contraction of the pupils, bradycardia, seizures, hypotonia with weak suck, and Moro reflex. Stage 3 (severe): stupor, flaccidity, seizures, small pupils that react poorly to light, decreased stretch reflexes, hypothermia, and absent Moro reflex.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Neurodevelopmental disability Defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay, auditory and visual impairment.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antioxidants One RCT comparing allopurinol versus placebo added, which found no significant difference in mortality between groups. [13] However, there remains insufficient evidence to draw conclusions about the effects of antioxidants in infants with perinatal asphyxia, so categorisation unchanged (Unknown effectiveness).

REFERENCES

1. MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ* 1999;319:1054–1059.[PubMed]
2. Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998;317:1549–1553.[PubMed]
3. Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998;317:1554–1558.[PubMed]
4. Ellis M, Manandhar N, Manandhar DS, et al. Risk factors for neonatal encephalopathy in Kathmandu, Nepal, a developing country: unmatched case-control study. *BMJ* 2000;320:1229–1236.[PubMed]
5. Levene ML, Kornberg J, Williams TH. The incidence and severity of post-asphyxial encephalopathy in full-term infants. *Early Hum Dev* 1985;11:21–26.[PubMed]
6. Thornberg E, Thiringer K, Odeback A, et al. Birth asphyxia: incidence, clinical course and outcome in a Swedish population. *Acta Paediatr* 1995;84:927–932.[PubMed]
7. Airede AI. Birth asphyxia and hypoxic-ischaemic encephalopathy: incidence and severity. *Ann Trop Paediatr* 1991;11:331–335.[PubMed]
8. Oswyn G, Vince JD, Friesen H. Perinatal asphyxia at Port Moresby General Hospital: a study of incidence, risk factors and outcome. *P N G Med J* 2000;43:110–120.[PubMed]
9. Jones G, Steketee RW, Black RE, et al. How many child deaths can we prevent this year? *Lancet* 2003;362:65–71.[PubMed]
10. Whitelaw A. Systematic review of therapy after hypoxic–ischaemic brain injury in the perinatal period. *Semin Neonatol* 2000;5:33–40.[PubMed]
11. Van Bel F, Shadid M, Moison RM, et al. Effect of allopurinol on postasphyxial free radical formation, cerebral hemodynamics, and electrical brain activity. *Pediatrics* 1998;101:185–193.[PubMed]
12. Benders MJ, Bos AF, Rademaker CM, et al. Early postnatal allopurinol does not improve short term outcome after severe birth asphyxia. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F163–F165.
13. Gunes T, Ozturk MA, Koklu E, et al. Effect of allopurinol supplementation on nitric oxide levels in asphyxiated newborns. *Pediatr Neurol* 2007;36:17–24.[PubMed]

14. Wang XL, Yu SL, Yu T, et al. Treatment of neonatal hypoxic ischaemic encephalopathy (HIE) with compound *Salvia miltiorrhizae* and citicoline: a comparative study in China. *Singapore Paediatr J* 1997;39:120–123.
15. Inder TE, Volpe JJ. Mechanisms of perinatal brain injury. *Semin Neonatol* 2000;5:3–16.[PubMed]
16. Levene MI, Gibson NA, Fenton AC, et al. The use of a calcium-channel blocker, nicardipine, for severely asphyxiated newborn infants. *Dev Med Child Neurol* 1990;32:567–574.[PubMed]
17. Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004.
18. Altman DI, Young RS, Yagel SK. Effects of dexamethasone in hypoxic–ischemic brain injury in the neonatal rat. *Biol Neonate* 1984;46:149–156.[PubMed]
19. Levene MI, Evans DH. Medical management of raised intracranial pressure after severe birth asphyxia. *Arch Dis Child* 1985;60:12–16.[PubMed]
20. Kecskes Z, Healy G, Jensen A. Fluid restriction for term infants with hypoxic–ischaemic encephalopathy following perinatal asphyxia. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004. Primary sources Cochrane Central Register of Controlled Trials, Medline, CINAHL, Oxford Database of Perinatal Trials, previous reviews, including cross-references and abstracts.
21. Donn SM, Goldstein GW, Schork MA. Neonatal hypoxic–ischemic encephalopathy: current management practices. *J Perinatol* 1988;8:49–52.[PubMed]
22. Jacobs S, Hunt R, Tarnow-Mordi W, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003; primary sources Oxford Database of Perinatal Trials, Cochrane Central Register of Controlled Trials, Medline, previous reviews including cross-references, abstracts, conferences, symposia proceedings, expert informants, and journal hand searching.
23. Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. *Pediatr Neurol* 2005;32:11–17.[PubMed]
24. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005;365:663–670.[PubMed]
25. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. *N Engl J Med* 2005;353:1574–1584.[PubMed]
26. Westin B, Miller JA, Nyberg R,et al. Neonatal asphyxia pallida treated with hypothermia alone or with hypothermia and transfusion of oxygenated blood. *Surgery* 1959;45:868–879.[PubMed]
27. Thoresen M, Penrice J, Lorek A, et al. Mild hypothermia after severe transient hypoxia–ischemia ameliorates delayed cerebral energy failure in the newborn piglet. *Pediatr Res* 1995;37:667–670. [PubMed]
28. Laptook AR, Corbett R, Sterett R, et al. Modest hypothermia provides partial neuroprotection when used for immediate resuscitation after brain ischemia. *Pediatr Res* 1997;42:17–23.[PubMed]
29. Higgins RD, Raju TN, Perlman J, et al. Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop. *J Pediatr* 2006;148:170–175.[PubMed]
30. Liu Z, Xiong T, Meads C. Clinical effectiveness of treatment with hyperbaric oxygen for neonatal hypoxic ischaemic encephalopathy: a systematic review of the Chinese literature. *BMJ* 2006;333:374.[PubMed]
31. Rosenberg AA. Response of the cerebral circulation to hypocarbia in postasphyxia newborn lambs. *Paediatr Res* 1992;32:537–541.[PubMed]
32. Hunt R, Osborn D. Dopamine for prevention of morbidity and mortality in term newborn infants with suspected perinatal asphyxia. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002; primary sources Oxford Database of Perinatal Trials, Cochrane Controlled Trials Register, Medline, previous review, including cross-references, abstracts, conferences, and symposia proceedings.
33. Ichiba H, Tamai H, Negishi H, et al. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. *Pediatr Int* 2002;44:505–509.[PubMed]
34. Adhikari M, Moodley M, Desai PK. Mannitol in neonatal cerebral oedema. *Brain Dev* 1990;12:349–351.[PubMed]
35. McGuire W, Fowlie PW, Evans DJ. Naloxone for preventing morbidity and mortality in newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003. Primary sources Cochrane Central Register of Controlled Trials, Medline, Embase, conference proceedings, and previous reviews.
36. Chernick V, Manfreda J, De Booy V, et al. Clinical trial of naloxone in birth asphyxia. *J Pediatr* 1988;113:519–525.[PubMed]
37. Saugstad OD, Ramji S, Vento M. Resuscitation of depressed newborn infants with ambient air or pure oxygen: a meta-analysis. *Biol Neonate* 2005;87:27–34.[PubMed]
38. Rootwelt T, Odden JP, Hall C, et al. Cerebral blood flow and evoked potentials during reoxygenation with 21 or 100% O2 in newborn pigs. *J Appl Physiol* 1993;75:2054–2060.[PubMed]
39. Evans DJ, Levene MI. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2001. Primary sources Medline, Embase, CCTR, and hand searches of conference abstracts.
40. Singh D, Kumar P, Narang A. A randomized controlled trial of phenobarbital in neonates with hypoxic ischemic encephalopathy. *J Matern Fetal Neonatal Med* 2005;18:391–395.[PubMed]

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GRADE **Evaluation of interventions for Perinatal asphyxia.**

Important outcomes			Mortality, Neurological impairment						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions in term or near-term newborns with perinatal asphyxia?									
3 (114) [11] [12] [13]	Mortality	Allopurinol versus placebo or no drug treatment	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for composite outcome in one RCT
1 (60) [13]	Neurological impairment	Allopurinol versus placebo or no drug treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (63) [14]	Mortality	Miltiorrhizae versus citicoline (cytidine diphosphate choline)	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, and for allocation, blinding, and randomisation flaws. Directness point deducted for composite outcome
4 (559) [22] [23] [24] [25]	Mortality	Head, and whole-body, hypothermia versus normothermia	4	0	0	–1	0	Moderate	Directness point deducted for the use of composite outcome in three RCTs
2 (231) [22] [25]	Neurological impairment	Head, and whole-body, hypothermia versus normothermia	4	0	0	0	0	High	
7 (675) [30]	Mortality	Hyperbaric oxygen treatment	4	–3	0	0	0	Very low	Quality points deducted for poor follow-up, and for allocation, blinding, and randomisation flaws
7 (649) [30]	Neurological impairment	Hyperbaric oxygen treatment	4	–3	0	0	0	Very low	Quality points deducted for poor follow-up, and for allocation, blinding, and randomisation flaws
1 (33) [33]	Mortality	Magnesium sulphate plus inotrope support versus no drug treatment	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for composite outcome
1 (25) [34]	Mortality	Mannitol versus no drug treatment	4	–2	0	0	0	Low	Quality points deducted for sparse data and wide confidence intervals
5 (1737) [37]	Mortality	Resuscitation in air versus pure oxygen	4	–3	0	0	0	Very low	Quality points deducted for poor follow-up, and for allocation, blinding, and randomisation flaws
4 (155) [39] [40]	Mortality	Prophylactic anticonvulsants versus no drug treatment	4	–3	0	0	0	Very low	Quality points deducted for sparse data, allocation and blinding flaws, and lack of placebo control
2 (155) [39] [40]	Neurological impairment	Prophylactic anticonvulsants versus no drug treatment	4	–3	0	0	0	Very low	Quality points deducted for sparse data; methodological, allocation, and blinding flaws; and lack of placebo control

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.